Pembrolizumab in endometrial cancer: Where we stand now (Review)

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Abstract. Recently, immunotherapy has shown promising results in solid tumors. To the best of our knowledge, this is the first systematic review of published literature synthesizing all the available data and evaluating both the efficacy and safety of pembrolizumab in endometrial cancer. The present study was performed in accordance with the PRISMA guidelines. Eligible articles were identified by searching the MEDLINE and ClinicalTrials.gov databases, using a predefined combination of the terms 'endometrial cancer' and 'pembrolizumab'. Overall, nine articles incorporating data from 712 patients were eligible. Pembrolizumab was demonstrated to be an effective and safe therapeutic option for the management of advanced/metastatic endometrial cancer. Results of ongoing trials evaluating either pembrolizumab alone or in combination with other antineoplastic regimens are expected to confirm its efficacy in this setting of patients. Pembrolizumab appears to be both durable and robust in endometrial cancer. However, there is an emerging need for novel predictive biomarkers to guide clinical practice.

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1. Introduction

Endometrial cancer (EC) is the most common gynecological malignancy accounting for approximately 61,880 new cases and 12,160 deaths in the United States (1). Metabolic syndrome, diabetes mellitus, Lynch syndrome, hormone therapy and tamoxifen use are the main risk factors for endometrial cancer (2). Most ECs are identified at an early stage (75%), however ~25% of ECs are diagnosed at a late stage. Prognosis for advanced disease remains poor; 5-year survival rates are <50% for patients with lymph node involvement and <20% for patients with peritoneal or distant metastases (3). Indeed, 5-year survival ranges from 91% for FIGO IA disease to as low as 47% for FIGO IIIC and 17% for FIGO IV disease.

Chemotherapy with carboplatin plus paclitaxel has gradually replaced the triple drug combination of cisplatin, doxorubicin and paclitaxel and is currently the standard of care in the metastatic setting (4,5). Hormone treatment with progestins, anti-estrogens and aromatase inhibitors are associated with low response rates (30%) (6,7). Nevertheless, options are limited for patients progressing on first line treatment highlighting the need for novel treatment regimens (8).

The interaction between tumor cells and T cells has been well established. Immune response is mediated by the interaction of the MHC-peptide complex with the T-cell receptor (TCR) and the binding of the co-stimulatory receptor CD28 on T cells with the ligand B7 on antigen-presenting cells (APCs) (9). In order to avoid autoimmune response cytotoxic T lymphocyte antigen-4 (CTLA-4) binds to CD28 and acts as a competitor for B7. Respectively, the programmed death 1 (PD-1) inhibitory receptor is expressed by T cells and binds to two ligands, namely programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) within the tumor microenvironment (10). This blockade enables the escape of tumor cells from immunosurveillance by inhibiting the activation of T cells and suppressing the T cell-mediated tumor cytolysis (11,12). Both PD-1 and PD-L1 are targets of immunotherapeutic drugs which block their interaction and promote durable responses in a variety of cancer types (13,14).

High expression of PD-L1 seems to be a predictive biomarker for anti-PD1 therapy, although some PD-L1 negative cancers may also respond to this kind of treatment (15-17). EC cells may activate the PD-1/PD-L1 signaling pathway since they overexpress PD-L1 receptor in 25 to 100% of cases (18).

Historically, endometrial carcinoma has been classified into two main clinicopathological and molecular types: type I which includes endometrioid adenocarcinomas (80-90%) and type II which includes non-endometrioid subtypes such as serous, clear-cell and undifferentiated carcinomas as well as carcinosarcoma (10-20%) (2). The Cancer Genome Atlas (TCGA) Research Network proposed a different molecular classification of EC that divided EC tumors into four subgroups: i) POLE ultra-mutated, ii) microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR), III) low copy number with low mutation rate, iv) high copy number with high mutation rate (19). According to TCGA Research Network some EC subtypes like POLE mutated cancers and MSI-H/dMMR groups are characterized by an immunogenic tumor microenvironment and express high level of immune checkpoint-associated proteins including PD-L1 (19).

Given the immunogenic profile of these molecular subtypes and the overexpression of PD-L1 in EC cells, monoclonal anti-PD-1 pembrolizumab could prove to be an efficient novel treatment in EC. This is the first systematic review of the literature to synthesize data from recent and ongoing clinical trials regarding the efficacy and safety of pembrolizumab in EC.

2. Sources and study selection

This systemic review was performed according to PRISMA guidelines (20). The protocol has been submitted to the Institutional Review Board of Alexandra University Hospital and is available upon request. Eligible articles were identified by a search of MEDLINE and Clinicaltrials.gov databases for the period up to 05/28/2021. The search strategy included the following keywords: ((endometrial) AND (neoplasm OR cancer OR carcinoma)) AND (pembrolizumab).

English - language restrictions were applied. Two investigators Aravantinou Fatorou A (AFA) and Andrikopoulou A (AA) working independently searched the literature and extracted data from each of the eligible studies. Clinical trials were considered eligible for our study, while reviews and case reports were excluded. In order to maximize the amount of synthesized information, we systematically examined the reference lists of the articles retrieved to identify potentially eligible studies and/or conference abstracts.

Eligible articles included all studies evaluating the efficacy and safety of pembrolizumab in EC no matter of sample size. For each of these studies, the following data were collected: first author, year of publication, phase of the trial, number of patients enrolled, disease setting (metastatic etc.), overall response rate (ORR) including complete response (CR) rate and partial response (PR) (%), stable disease (SD) rate (%), progression disease (PD) rate (%), median overall survival (mOS) in months, median progression free survival (mPFS) in months, data regarding biomarker analysis and adverse events. From multicohort trials, the number of patients with EC was identified and only data addressing this population were included in our study.

3. Data on efficacy and safety

The search strategy retrieved 72 articles. Overall, 18 reviews (21-38) and 8 case reports (39-46) were identified, while 40 studies were deemed irrelevant. After removal of ineligible studies, 6 studies were recruited (47-52). After evaluating the references of the eligible studies, three additional articles were identified (53-55). Overall, 9 studies incorporating data from 712 EC patients were eligible for this systematic review (47-55). The aforementioned process of the selection of studies is illustrated in Fig. 1. Table I presents an overview of all the ongoing or completed clinical trials with published results investigating the efficacy and safety of pembrolizumab in endometrial cancer.

Five out of nine trials were multicohort including a variety of MSI-H/ dMMR deficient tumors (47,48,51,52,55) while four trials enrolled exclusively endometrial cancer patients (49,50,53,54). Six clinical trials were Phase Ib/II (47,49,51-53,55), one was Phase III (54) randomized clinical trial, while two of them were retrospective, single-institution cohort studies (48,50).

All patients had histologically or cytologically confirmed locally advanced, metastatic or recurrent EC. They had received at least one previous systematic treatment and had evidence of disease progression (47-55). Five studies evaluated pembrolizumab administration in patients with MSI-H/dMMR advanced EC (48,49,52,53,55), one study focused on PD-L1 positive EC patients (47), while the other studies evaluated pembrolizumab administration in advanced EC irrespective of MSI or PD-L1 status (50,51,54). Three studies evaluated the combination of pembrolizumab with lenvatinib in advanced/recurrent EC (50,51,54) whereas the remaining studies evaluated pembrolizumab as a single agent in pretreated PD-L1 positive and/or MSI-H/dMMR advanced EC tumors (47-49,52,53,55).

664 patients received pembrolizumab 200 mg intravenously every three weeks (48-52,54) whereas 48 patients received pembrolizumab at a dose of 10 mg/kg every two weeks (47,53,55). Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) with computer tomography (CT) or magnetic resonance (MRI) per study protocol.

Objective Response Rate (ORR) was calculated in all of the trials identified (47-55).

In PD-L1 positive advanced or recurrent EC cancer, ORR is 13% (95% CI; 2.8-33.6%) (NCT02054806) (47). Median PFS was 1.8 months (95% CI; 1.6-2.7) while median OS was not reached (95% CI; 4.3-NR).

In MSI-H/dMMR advanced EC patients with disease progression on prior standard treatment ORR was 55.9% (57/102) (48,49,52,53,55). Median PFS and OS were reported only in one study (NCT02628067) (52). Median PFS was 25.7 (95% CI; 4.9-NR) while median OS was not reached (95% CI; 27.2-NR). 12-month OS was reported in two studies and was 73-89% (52,53,56). Of note, 79% of patients with MSI-H/dMMR EC with change from baseline exhibited a reduction in tumor size, while in 70% of patients the reduction was greater than 30% (52,56).

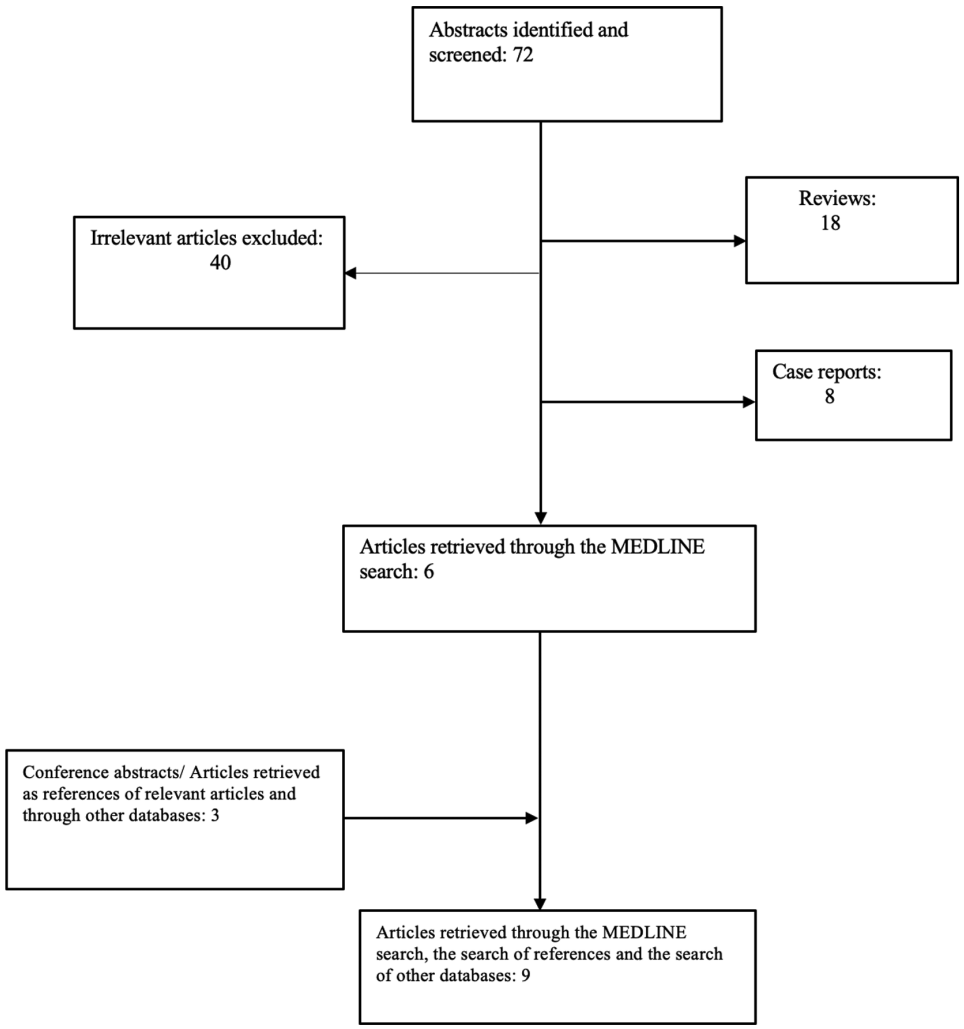

Figure 1. Stages of the search strategy.

For patients receiving the combination of pembrolizumab with lenvatinib for previously treated advanced/recurrent EC, ORR was 38.4% (63/164) with 6.7% of patients achieving CR (11/164) and 31.7% of PR (52/164) (50,51). In KEYNOTE-146 (NCT02501096), median PFS was 7.4 months (95% CI; 5.3-8.7), while median OS was 16.7 months (95% CI; 15-NR) (51). In Phase III KEYNOTE-775 trial of Lenvatinib plus pembrolizumab versus treatment of physician's choice, mPFS was 7.2 months and mOS was 18.3 months in agreement with previous results (54). Of note, ORR was higher in MSI-H/dMMR advanced EC patients. How *et al* (50) demonstrated that a lower starting dosage of lenvatinib than the recommended dose of 20 mg was equally effective (response rates: 23.1 vs. 41.9%; P=0.56).

Safety profile. Pembrolizumab was administered as a single agent in six studies (47-49,52,53,55). Safety data were reported in four of these studies [NCT02054806, NCT02628067, NCT01876511, Choi *et al* (48)] (47,48,52,55). Treatment-related adverse events (TRAEs) of any grade were reported in 66% (246/372) of patients and 15.6% (58/372) of patients experienced grade 3/4 TRAEs. The most common treatment related AEs were fatigue (16.9%; 63/372), pruritus (17.2%; 64/372), arthralgia (9.1%; 34/372), diarrhea (12.9%; 48/372), asthenia (7.3%; 27;372) and hypothyroidism (11%; 41/372). In all studies, there was only one case of suspected treatment-related mortality in a patient with interstitial lung disease (48).

The safety profile of pembrolizumab plus lenvatinib combination was reported in two studies (NCT02501096, NCT03517449) (51,54). In KEYNOTE-146 trial, any-grade TRAEs occurred in 96.8% (120/124) of patients and grade ≥3 TEAEs occurred in 66.9% (83/124) of patients (51). In KEYNOTE-775, grade ≥3 TEAEs were reported in 89% of patients. Overall, 15.3-30.8% of patients discontinued lenvatinib, 12.1-18.7% discontinued pembrolizumab and 8.9-14% discontinued both study drugs due to treatment-related AEs. The most common TRAEs reported were: hypertension (59.7-64%), diarrhea (52.4-54%), hypothyroidism (43.5-57%) and nausea (38.7-50%). Of note, the recommended starting dose of 20mg lenvatinib treatment was associated with higher discontinuations (100 vs. 69.2%, P=0.01) and treatment interruptions (93.3 vs. 73.1%, P=0.09) compared with the lower starting dose of 14 mg (50).

4. Discussion

Generally, pembrolizumab administered either as a single agent or in combination with other compounds is a safe and well-tolerated drug for multiple solid tumors (57,58). Molecular characterization of the tumor is a prerequisite for guiding

Table I. Summary of studies evaluating pembrolizumab in endometrial cancer.

First author/s, year	Trial no.	Phase	Study year	No. of patients	Cancer type	Compound	Dose schedule	Median age, years	Histology	Clinical response	Adverse events	(Refs.)
Ott *et al*, 2017	NCT02054806	1b	2017	24	Locally advanced/ metastatic PD-L1-positive EC	Pembrolizumab	10 mg/kg q2weeks	67	Endometrioid adenocarcinoma: 17 (70.8%) Adenocarcinoma other: 3 (12.5%) High-grade serous: 2 (8.3%) Carcinosarcoma: 1 (4.2%)	PR :3 (13%) SD:3 (13%) PD: 13 (56.5%) ORR:13% mPFS:1.8 months mOS: Not reached	TRAEs: 13/24 (54.2%) Gr3/4 TRAEs: 4/24 (16.7%) Fatigue (5; 20.8%) Pruritus (4; 16.7%) Pyrexia (3; 12.5%) Decrease appetite (3; 12.5%) Asthenia (2; 8.3%) Anemia (2; 8.3%) Arthralgia (2; 8.3%)	(47)
Marabelle *et al*, 2020	NCT02628067	2	2019	49	Advanced/ metastatic MSI-H/ dMMR EC	Pembrolizumab	200 mg q3weeks	65	Endometrioid (53%) Adenocarcinoma (43%) Clear cell (2%) Mucinous (2%)	CR:8 (16%) PR:20 (41%) SD: 8 (16%) ORR: 57.1% mPFS: 25.7 months mOS: Not reached	TRAEs: 151/233 (64.8%) Fatigue (34; 14.6%) Nausea (15; 6.4%) Diarrhea (28; 12%) Pruritus (30; 12.9%) Asthenia (25; 10.7%) Hypothyroidism (19; 8.2%) Arthralgia (18; 7.7%)	(52)
Le *et al*, 2017	NCT01876511	2	2017	15	Advanced/ metastatic MSI-H/ dMMR EC	Pembrolizumab	10 mg/kg q2weeks	NR	NR	CR: 3 (20%) PR: 5 (33%) SD: 3 (20%) ORR: 53% DCR: 73% PFS: NR OS: NR	TRAEs: 62/84 (74%) Gr3/4 TRAEs: 34 (14.6%) Pruritus (30; 36%) Fatigue (21; 25%) Diarrhea (19; 23%) Pruritus (30; 36%) Thyroid disease/(18; 21%) hypophisitis Arthritis (14; 17%) Nausea (11; 13%) Anemia (6; 7%)	(55)
Fader *et al*, 2016	NA	2	2016	9	Advanced/ recurrent dMMR EC	Pembrolizumab	10 mg/kg q2weeks	NR	Endometrioid (100%)	PR: 4 (44.4%) CR :1 (11.1%) ORR: 56% DCR: 88.9% mOS: Not reached	NR	(53)

Table I. Continued.

First author/s, year	Trial no.	Phase	Study year	No. of patients	Cancer type	Compound	Dose schedule	Median age, years	Histology	Clinical response	Adverse events	(Refs.)
Roque *et al*, 2021	NCT02899793	2	2021	24	Advanced/ metastatic MSI-H/ dMMR EC	Pembrolizumab	200 mg q3weeks	NR	NR	ORR: 58%	NR	(49)
Makker *et al*, 2020	NCT02501096	1b/2	2020	108	Advanced/ metastatic EC	Pembrolizumab; lenvatinib	200 mg; 20 mg/day q3weeks	65.1	Endometrioid (50.9%)	CR: 8 (7.4%)	TRAEs: 120 (96.8%) Hypertension (61.1%) Diarrhea (52.8%) Fatigue (51.9%) Decreased appetite (47.2%) Hypothyroidism (44.4%) Nausea (39.8%) Stomatitis (33.3%) Pain/arthralgia (31.5%)	(51)
										PR: 34 (31.5%)	Dysphonia (27.8%)	
										SD: 49 (45.4%)	Vomiting (26.9%)	
										PD: 12 (11.1%)	Skin reactions (26.9%)	
									Serous adenocarcinoma (32.4%)	ORR: 38.9%		
									Clear cell (5.6%)	DCR: 84.3%		
									Undifferentiated (0.9%)	mPFS: 7.4 months		
									Adenocarcinoma other (0.9%)	mOS: 16.7 months		
How, 2021	NA	Single-institution, retrospective	2021	67	Advanced/ metastatic EC	Pembrolizumab; lenvatinib	NR; 20 vs. <20 mg/day	67	Endometrioid (19)	CR: 3/56 (5.4%)	NR	(50)
									Serous adenocarcinoma (19)	PR: 18/56 (32.1%)		
									Carcinosarcoma (13)	ORR: 21/56 (37.5%)		
									Clear cell (4)	SD: 18/56 (32.1%)		
									Mixed (8)			
									Other (4)			
Makker, 2021	NCT03517449	3	2021	827	Advanced/ metastatic EC	Pembrolizumab plus lenvatinib vs. doxorubicin or paclitaxel	200 mg q3weeks; 20 mg/day; 60 mg/m^2 Q3W; 80 mg/m^2 QW	NR	NR	ORR: 31.9 vs. 14.7%	TRAEs Gr3/4/5: 89% Hypertension (64%) Diarrhea (54.2%) Nausea (50%) Decreased appetite (44.8%) Hypothyroidism (57.4%) Vomiting (36.7%) Weight loss (34%) Fatigue (33%)	(54)

Table I. Continued.

First author/s, year	Trial no.	Phase	Study year	No. of patients	Cancer type	Compound	Dose schedule	Median age, years	Histology	Clinical response	Adverse events	(Refs.)
										CR: 6.6% PR: 25.3% mPFS: 7.2 vs. 3.8 months; HR: 0.56 mOS: 18.3 vs. 11.4 mo; HR: 0.62	Arthralgia (30.5%) Proteinuria (28.8%) Anemia (26.1%) Constipation (25.9%)	
Choi *et al*, 2020	NA	Single-institution, retrospective	2020	5	Advanced/ metastatic MSI-H/ dMMR EC	Pembrolizumab	200 mg q3weeks	NR	High-grade serous (20%)	CR: 1 (20%)	TRAEs: 20/31; 64.5% Gr3/4/5 TRAEs: 3/31; 9.7% Hypothyroidism (4; 12.9%) Anemia (4; 12.9%) Fatigue (3; 9.7%) Renal insufficiency (2; 6.5%) Rash (1; 3.2%) Thrombocytopenia (1; 3.2%) Anorexia (1; 3.2%)	(48)
									Carcinosarcoma (20%) Neuroendocrine carcinoma (20%) Leiomyosarcoma (20%) Dedifferentiated (20%)	PR: 1 (20%) PD: 3 (60%) ORR: 40%	Diarrhea (1; 3.2%)	

EC, endometrial cancer; ORR, objective response rate; CR, complete response; PR, partial response; PD-L1, programmed death ligand-1; mPFS, median progression-free survival; mOS, median overall survival; dMMR, mismatch repair-deficient; MSI-H, high microsatellite instability; TRAEs, treatment-related adverse events; DCR, disease control rate; NR, not reported; NA, not applicable; , SD, stable disease; OS, overall survival.

Table II. Ongoing clinical trials of pembrolizumab in endometrial cancer.

Trial	Registration no.	Phase	Study population	Estimated enrollment, n	Status	Treatment regimens	Estimated completion year
-	NCT04214067	3	Newly diagnosed early stage (stage I/II) high/intermediate risk dMMR EC	168	Recruiting	Pembrolizumab plus radiation (EBRT and vaginal brachytherapy) vs. radiation treatment	2024
LEAP-001	NCT03884101; NCT04865289	3	Advanced (stage III/IV) or recurrent EC	875	Active, not recruiting	Pembrolizumab plus lenvatinib vs. chemotherapy (carboplatin/paclitaxel)	2023
KEYNOTE-775 (85.5)	NCT03517449	3	Advanced/recurrent EC	827	Active, not recruiting	Pembrolizumab plus lenvatinib vs. physician's choice (paclitaxel or doxorubicin)	2023
-	NCT03914612	3	Advanced (stage III/IV) or recurrent EC	810	Recruiting	Pembrolizumab plus carboplatin/paclitaxel vs. placebo plus carboplatin/paclitaxel	2023
KEYNOTE-B21	NCT04634877	3	Newly diagnosed high risk EC (stage III/IVA or stage I/II with myometrial invasion or stage I/II with myometrial invasion with aberrant p53 expression/mutation)	990	Recruiting	Pembrolizumab plus chemotherapy (carboplatin plus paclitaxel/docetaxel) +/- radiation vs. placebo plus chemotherapy (carboplatin plus paclitaxel/docetaxel) +/- radiation	2025
TOPIC	NCT03276013	2	Advanced/recurrent EC	48	Active, not recruiting	Pembrolizumab plus doxorubicin	2021
-	NCT03835819	2	Microsatellite stable (MSS) advanced or recurrent EC	35	Recruiting	Pembrolizumab plus mirvetuximab soravtansine	2023
-	NCT02501096	01-Feb	Metastatic solid tumors (EC, RCC, NSCLC, melanoma, urothelial, HNSCC)	357	Active, not recruiting	Pembrolizumab plus lenvatinib	2023
-	NCT02899793	2	Metastatic or recurrent hypermutated/ ultramutated (MMR deficient) EC	25	Active, not recruiting	Pembrolizumab	2022
-	NCT02549209	2	Adavanced or recurrent EC	46	Active, not recruiting	Pembrolizumab plus carboplatin/paclitaxel	2021
KEYNOTE-158	NCT02628067	2	Advanced solid tumors (EC, biliary, cervical, thyroid, vulvar, anal cancer, SCLC, salivary gland, parotid cancer, etc.)	1595	Recruiting	Pembrolizumab	2026
PRIMMO	NCT03192059	2	Advanced or recurrent EC, cervical cancer or uterine sarcoma	43	Recruiting	Immunomodulatory cocktail (vitamin D, aspirin, cyclophosphamide and lansoprazole),followed by pembrolizumab plus radiation	2022
-	NCT04197219	2	Recurrent MSI-H/dMMR EC	0	Withdrawn	Pembrolizumab plus axitinib	
-	NCT04781088	2	Recurrent EC, epithelial ovarian, fallopian tube or primary peritoneal cancer	47	Not yet recruiting	Lenvatinib plus pembrolizumab plus paclitaxel weekly	2024
ATAPEMBRO	NCT04014530	01-Feb	Metastatic deficient/proficient CRC and MMR deficient EC	47	Recruiting	Pembrolizumab plus ataluren	2023
GYNET (64)	NCT04652076	01-Feb	Advanced/recurrent EC or cervical cancer	240	Recruiting	NP137 plus carboplatin/ paclitaxel and/or pembrolizumab	2024
FIGHT-101	NCT02393248	01-Feb	Advanced malignancies with genetic alterations in FGF or FGFR genes (EC, lung cancer, BC, gastric cancer, urothelial cancer, etc.)	201	Active, not recruiting	Pemigatinib FGFR inhibitor (INCB054828) plus pembrolizumab or pemigatinib plus other treatment regimens (docetaxel, trastuzumab, gemcitabine/cisplatin, retifanlimab)	2021

Table II. Continued.

Trial	Registration no.	Phase	Study population	Estimated enrollment, n	Status	Treatment regimens	Estimated completion year
-	NCT04278144	01-Feb	HER2-expressing advanced malignancies refractory to available treatment (BC, EC, gastric cancer, etc.)	390	Recruiting	BDC-1001 (anti-HER2 monoclonal antibody conjugated to a TLR 7/8 dual agonist) +/- pembrolizumab	2023
-	NCT01174121	2	Advanced or metastatic solid tumors refractory to standard chemotherapy (BC, ovarian cancer, EC, upper/lower gastrointestinal, hepatobiliary, genitourinary tumors or glioblastoma)	91	Suspended	Autologous tumor infiltrating lymphocytes (TILs) +/- pembrolizumab	2024
FIERCE (58)	NCT03932409	1	High/intermediate risk EC (grade 2/3 tumor, (+) lymphovascular space invasion, outer half myometrial invasion, etc.)	20	Recruiting	Pembrolizumab plus vaginal cuff brachytherapy (VCB) followed by pembrolizumab plus chemotherapy	2023
-	NCT03694834	1	Early stage, high grade obesity-driven EC	20	Recruiting	Pembrolizumab	2022
-	NCT04611139	1	Advanced or recurrent SWI/SNF-mutant gynecologic cancers [small cell ovarian cancer of the hypercalcemic type (SCCOHT), EC, ovarian clear cell tumor or ovarian endometrioid adenocarcinoma]	30	Not yet recruiting	Novel reversible LSD1 inhibitor SP-2577 (Seclidemstat) plus pembrolizumab	2023
-	NCT03454451	1	Advanced cancers (EC, NSCLC, RCC, CRC, TNBC, ovarian cancer, pancreatic cancer, head and neck SCC, NHL, etc.)	378	Recruiting	CPI-006 humanized monoclonal anti-CD73 antibody +/- Ciforadenant (adenosine 2A receptor antagonist) +/- pembrolizumab	2023
-	NCT04460456	1	Advanced HER2-expressing/amplified solid tumors refractory to available treatment (BC, EC, gastric cancer, CRC, TNBC, etc.)	294	Recruiting	SBT6050 (toll-like receptor (TLR) 8 agonist) +/- pembrolizumab	2024
-	NCT02521844	1	Advanced solid tumors refractory to available treatment (MSS-CRC, MSS-EC, MSS-ovarian cancer)	83	Recruiting	ETC-1922159 porcupine (PORCN) inhibitor +/- pembrolizumab	2023
-	NCT02630823	1	Surgically resectable stage III/IV EC	10	Completed	Pembrolizumab (2 doses) followed by surgery adjuvant chemotherapy (carboplatin/paclitaxel) followed by radiation and pembrolizumab	2020
-	NCT02728830	1	Gynecological cancers of Müllerian origin (epithelial ovarian, fallopian tube, primary peritoneal, or uterine endometrial cancer)	39	Active, not recruiting	Pembrolizumab	2021
FPA150-001	NCT03514121	1	Advanced solid tumors (BC, ovarian cancer, EC)	278	Active, not recruiting	Anti-B7H4 antibody FPA150 +/- pembrolizumab	2022
-	NCT02646748	1	Advanced solid tumors [EC, gastric cancer, melanoma, microsatellite unstable (MSI) colorectal cancer or other MMR-deficient tumors, NSCLC, RCC, head and neck SCC, TNBC, pancreatic cancer, etc.]	159	Active, not recruiting	JAK inhibitor itacitinib (INCB039110) plus pembrolizumab or PI3K-delta inhibitor (INCB050465) plus pembrolizumab	2021

NR, not reported; EC, endometrial cancer; BC, breast cancer; CRC, colorectal carcinoma; EBRT, external beam radiation therapy; MMR, mismatch repair; NP137, Humanized Monoclonal Antibody Targeting Netrin-1; BC, breast cancer; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; TNBC, triple negative breast cancer; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; MSS, microsatellite stable.

therapeutic selection of pembrolizumab in EC patients. All the ongoing clinical trials with pembrolizumab as a single agent or in combination with other treatment regimens are presented in Table II.

As already discussed, KEYNOTE-146 Phase Ib/II basket trial evaluated the combination of lenvatinib plus pembrolizumab in patients with advanced EC, regardless of PD-L1 or MSI status (51). Lenvatinib is an oral multikinase inhibitor of the vascular endothelial growth factor receptors (VEGFR)1-3, fibroblast growth factor receptors (FGFR)1-4, platelet-derived growth factor receptor-α (PDGFR-α), RET, and KIT (59-61). On September 17, 2019 the FDA granted accelerated approval to pembrolizumab plus lenvatinib for the treatment of patients with advanced non-MSI-H/dMMR EC who exhibited disease progression to prior systemic therapy and are not candidates for curative surgery or radiation.

Two phase III, randomized, clinical trials (NCT03517449, NCT03884101) were designed to compare this combination treatment with taxane-based chemotherapy in patients with advanced EC. Final data of KEYNOTE-775 are anticipated (54). LEEP-001 (NCT03884101) Phase III trial aims to compare the efficacy of pembrolizumab plus lenvatinib to standard chemotherapy (carboplatin plus paclitaxel) for the first-line treatment of advanced (Stage III/IV) or recurrent EC (62,63).

Adjuvant Radiation therapy (RT) is the treatment of choice for patients with early-stage EC and high risk of recurrence (64). Irradiated tumor cells secrete various factors that stimulate the activation of T cells and thus RT and immunotherapy may have a synergistic effect (65,66). A randomized Phase III study (NCT04214067) explores the addition of pembrolizumab to standard RT in patients with newly diagnosed early stage dMMR EC of high/intermediate risk (67).

PD-L1 tumor expression presents certain limitations as a predictive biomarker (68). Firstly, a standard cut off level is not yet established. Moreover, the interaction between tumor and immune cells is a dynamic process and therefore evaluating PD-L1 at a single time point may not directly corelate to response to anti-PD1 treatment (69). In addition, PD-L1 positive EC tumors showed only a modest response (13%) to anti-PD1 treatment compared to MSI-H/dMMR tumors (55.9%). Thus, it could not be safely speculated that patients with EC and high expression of PDL-1 will benefit more from pembrolizumab.

DNA mismatch repair (MMR) is a key DNA repair system that identifies erroneous bases during DNA replication and recombination. Microsatellites are short DNA sequences in which a motif of one to six bases is repeated (70). Potential errors to this region are repaired by DNA MMR genes. Both mismatch repair deficiency and high microsatellite instability have been proposed as predictive biomarkers of response to immune checkpoint inhibition. dMMR and MSI-H tumors comprise approximately the 30% of ECs (17-33%) (71). Thus, the use of MMR or/and MSI testing could be of importance in identifying patients with EC who will benefit from pembrolizumab.

DNA polymerase epsilon is a member of the DNA polymerase family that catalyzes the synthesis of DNA molecules and is essential for ensuring the fidelity of DNA replication (72). Mutations in POLE genes have been associated with high tumor mutational burden, elevated number of tumor-infiltrating and peritumoral lymphocytes, higher expression of PD-1 and PD-L1 (73) and consequently higher response rates to immunotherapy (72,74). POLE-mutated EC occurs in approximately 10% of EC cases (19). Ultra-mutated POLE ECs represent the 6.4% of low-grade and 17.4% of high-grade endometrioid tumors. Evaluation of POLE mutations may serve as an attractive predictive biomarker of susceptibility to immunotherapy (75).

Tumor mutational burden (TMB) is defined as the total number of somatic mutations per coding area. High TMB of at least 10 mutations per megabase was identified as a biomarker of favorable prognosis in KEYNOTE-158 study (76). ORR was achieved in 30 (29%; 95% CI: 21-39) of 102 patients in the TMB-high group versus 43 (6%; 95% CI: 5-8) of 688 participants in the non-TMB-high group, while duration of response was also longer in the first subgroup (not reached versus 33.1 months) (76). Overall, TMB could also serve as a biomarker of response to immune checkpoint treatment. All these potential biomarkers should be evaluated in large clinical trials before any conclusion is drawn.

To the best of our knowledge, this is the first systematic review evaluating the clinical role of pembrolizumab in EC patients. However, our study is characterized by certain limitations which should be highlighted. Eligible clinical trials were single arm, non-randomized, early Phase trials in the majority of cases (47-53,55).

5. Conclusion

Targeting PD-1 with pembrolizumab in pretreated patients with advanced or recurrent EC represents a promising therapeutic approach and has thus received two FDA approvals as a single agent and in combination with lenvatinib. Given the profound benefit of dMMR/MSI-H patients from immunotherapy, all patients should be tested for predictive biomarkers including MMR deficiency, MSI or PD-L1 expression to guide treatment selection. Ongoing randomized, Phase III clinical trials are warranted to confirm the clinical benefit of pembrolizumab in EC patients.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the Pubmed MEDLINE (https://pubmed.ncbi.nlm.nih.gov) and ClinicalTrials.gov databases (https://clinicaltrials.gov/ct2/home).

Authors' contributions

AAF wrote the manuscript and searched the literature. AA, OF and VEG searched the literature. FZ conceived the idea and

critically revised the manuscript and gave the final approval. ML, MG and MAD critically revised the manuscript and gave the final approval. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

FZ has received honoraria for lectures and has served in an advisory role for Astra-Zeneca, Daiichi, Eli-Lilly, Merck, Novartis, Pfizer and Roche. ML has received honoraria from Roche, Astra Zeneca, Astellas, MSD, Janssen, BMS and IPSEN. MG has received honoraria from Janssen, Genesis Pharm, Amgen, Karyopharm and Takeda. MAD has received honoraria and has served on advisory boards from Jannsen, Genesis Pharm, Amgen, Karyopharm and Takeda, outside the submitted work. AAF, AA, VEG and OF declare that they have no competing interests.

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